## REMARKS

The Amendments

Applicants have amended the title of the application to reflect the claims now pending. Applicants have also amended the cross-reference statement in the specification to perfect the priority claim of this continuation application, including adding reference to United States Application No. 07/110,255, filed on 20 October 1987, now abandoned, as reflected in the copy of the inventors' Declaration submitted on the filing date of this application. The cross-reference statement as amended also recites the status of the applications referred to therein. Additionally, applicants have amended the specification to indicate trademarked terms. Finally, applicants have amended the Abstract of the Disclosure to reflect in general the claims now pending.

Applicants have amended the claim 18 to recite a method of treating a coagulation disorder in a patient having an atherosclerotic plaque comprising administering to the patient a therapeutically effective amount of a lipoprotein associated coagulation inhibitor ("LACI"). Applicants have added dependent claims 19-26 reciting further embodiments of the method of claim 18, such as also administering another agent such as a thromobolytic agent. Support for amended claim 18 and added claims 19-26 can be found, *inter alia*, in the specification on page 9, lines 8-15; page 10, lines 4-8; page 13, line 29 to page 14, line 10; and page 16, line 9 to page 17, line 6. Claims 19-29 are now pending.

The Objections

The Examiner has objected to the title of the invention, the abstract of the disclosure and the cross-reference statement of the specification for reasons of record. Applicants have amended the application as requested by the Examiner. Applicants have also amended the application to indicate trademarked terms as requested by the Examiner.

The Rejections

(1) 35 U.S.C. 102(e)

The Examiner has rejected former claim 18 as being anticipated by Broze et al., (United States Patent No. 5,106,833) ("Broze"). First, the Examiner states that Broze teaches a method of inhibiting Factor Xa production or Factor VIIa/tissue factor enzymatic complex formation in a mammal with the coagulation inhibitor LACI and discloses the coagulation cascade in the Background section such that one of ordinary skill in the art would have immediately envisaged the treatment of a coagulation disorder as the target of the claimed patented methods at the time the invention was made. Applicants disagree.

To anticipate a claim, the reference must teach each and every element of the claim. MPEP 2131. Nowhere does Broze teach or mention that the inhibition of Factor VIIa/tissue factor enzymatic complex or, more specifically, the use of LACI as a drug, is useful for treating a single disease, much less a coagulation disorder. Broze methods amount to no more than a research method. Thus, Broze *per se* does not anticipate former claim 18 or amended claim 18, both of which recite a method of treating a disease using a therapeutically effective amount of LACI.

Second, the Examiner attempts to rectify the defects of Broze by referring to United States Application No. 07/077,366 ("Broze II"), an application from which Broze claims benefit and attempts to incorporate by reference. The Examiner states that Broze II provides LACI and its therapeutic use as a coagulation inhibitor and anti-thrombotic agent and a method for inhibiting factor Xa production or Factor VIIa/TF enzymatic complex formation with intact tissue factor inhibitor. The Examiner remarks that the instant claim language or limitations do not appear to result in a manipulative difference in the method steps when compared to the prior art disclosure. Applicants traverse.

Broze II's sole reference to any therapeutic use is on page 3, lines 13-15.[1] This exact sentence was cancelled from Broze I. MPEP 2136.02 states that portions of the patent application which were cancelled are not part of the patent or application publication and thus

[1] "In particular, the novel TFI of this invention has indicated therapeutic use as a coagulation inhibitor and anti-thrombotic agent."

cannot be relied on in a 35 U.S.C. 102(e) rejection over the issue patent or application publication. Thus, the content of this statement is not available against former claim 18 or amended claim 18 as prior art. Even if the statement had not been deleted in total (which it was), it would not have been suitable for incorporation under the criterias for essential and non-essential material described in MPEP 608.01(p) in view of Broze I's claimed invention.

The only other reference to a step of administering LACI to a living thing in Broze II is in claims 5-6 (page 35 of Broze II). These claims do not add to the statements of Broze I. Like Broze I, this method does not refer to any disease, therapeutically effective amount or the desire to use the method to treat a disease. Neither Broze I nor Broze II (excluding the cancelled theraputic use) propose to treat a population that has an affiction or illness. Former claim 18 and amended claim 18 of the present application, on the other hand, do recite method steps that are distinct from the prior art disclosure - e.g., both recite the treatment of a disorder in a patient with a therapeutically acceptable amount of LACI. Thus, former claim 18 and amended claim 18 are not anticipated by Broze I alone or in combination with subject matter incorporated from Broze II.

Nonetheless, to expedite prosecution, applicants have amended claim 18 to recite that the patients to be treated have an atherosclerotic plaque. As discussed above, the concept of treating a patient, generally or specifically, is not described in Broze I or Broze II. Further, nowhere in Broze I or Broze II are Broze I is atherosclerosis or patients having atherosclerotic plaques mentioned, taught or suggested. Thus, amended claim 18 cannot be not anticipated by Broze I alone or in combination with subject matter incorporated from Broze II.

(2) 35 U.S.C. 103(a)

The Examiner has rejected former claim 18 as being unpatentable over Broze I in view of Broze et al., (1987) *PNAS* 84:1886-1990 ("Broze III") and/or Broze et al., (1988) *Blood* 71:335-343 ("Broze IV"). Specifically, with regard to Broze I, the Examiner provides the same statements that applicants have addressed above. The Examiner states that Broze III teaches the isolation of LACI and teaches that Factor VII-tissue factor pathway of coagulation is involved in several pathological conditions associated with disordered coagulation and thrombosis. The

Examiner remarks that Broze IV teaches that LACI inhibits Factors VIIa-tissue factor and plays an important role in the in vivo coagulation and is useful in treatment. Applicants traverse.

First, as discussed above, the subject matter of Broze II should not be prior art against this application because the relevant subject matter was cancelled from the published patent Broze I and, regardless, is not suitable for incorporation. If anything, deletion of the therapeutic use statement from Broze I may be considered to teach away from the use of LACI as a therapeutic.

Second, as discussed above, Broze I *per se* does not teach or disclose the use of LACI to treat a patient having an affliction or illness.

Third, Broze III does not correct the defect in Broze I. Broze III discusses a method of purifying a protein referred to as "TFI" from humans. No sequence information for TFI was provided in Broze III. Contrary to the Examiner's statement, Broze III does not teach that Factor VII-tissue factor pathway is involved in several pathological conditions. Rather, Broze III states that Factor VII-tissue factor pathway may also be involved several pathological conditions - i.e., the mechanism might be involved in some conditions. Thus, neither Broze III alone nor in combination with Broze I teaches or suggests the use of LACI , which inhibits tissue factor activity, as a drug for treating a disease.

Fourth, Broze IV does not correct the defect in Broze I. Broze IV discusses studies relating to a possible mechanism of action for LACI (title of Broze IV). Contrary to the Examiner's assertion, Broze IV does not state that LACI plays an important role in vivo coagulation; Broze IV states that LACI probably plays an important role *in vivo* coagulation (abstract of Broze IV). Furthermore, Broze IV states that LACI "appears" to play a role in a novel feedback inhibition system (page 342, col. 2 of Broze IV). Thus, Broze IV at the most opines on whether there is a role for LACI *in vivo coagulation* and, if so, the importance of the role. Broze IV makes no mention that that LACI is useful as a drug for treating a disease. Neither Broze IV alone nor in combination with Broze I teaches or suggests the use of LACI as a drug for treating a disease.

Fifth, Broze I, Broze III and Broze IV in combination do not mention, teach or suggest the use of LACI as a drug for treating a disease.

Six, regardless of the individual disclosures of Broze II and Broze III, applicants point out that Broze I, which application was filed after the publication of Broze II and Broze III, no longer contains a therapeutic use statement. Thus, if anything, in view of the totality of the art, Broze I teaches away from a therapeutic use for LACI by its omission.

Finally, to establish a *prima facie* case of obviousness, three basic criteria must be met (MPEP 2142). First, there must be some suggestion or motivation to modify the reference or to combine reference teachings. As discussed above, none of the Broze references alone or in combination provide a suggestion or motivation to modify Broze I to use LACI as a drug for treating a disease - - Broze III and Broze IV relate to whether LACI plays a role in vivo coagulation at all and if so to what extent. Second, there must be a reasonable expectation of success. Again, the references alone or in combination do not hint or suggest that there would be a reasonable expectation of success in patients given that the role of LACI in *in vivo* coagulation was being studied. Third, the prior art reference (or references when combined) must teach or suggest all the claimed limitations. This has not been done. None of Broze I, Broze III or Broze mention the therapeutic use of LACI as a drug. Thus, the Examiner has not put forth a *prima facie* case of obviousness for former claim 18.

That being said, claim 18 as amended, states that the patient to be treated has an atherosclerotic plaque. The instant specification teaches *inter alia* that (a) there is significant synthesis of tissue factor protein in atherosclerotic plaques, (b) that tissue factor protein accumulates in the necrotic core and is found in foam cell rich regions of the plaque; and (c) that there is in the plaque procoagulant activity due to tissue factor (page 13, lines 17-23 of the specification as filed). The instant specification also teaches that tissue factor protein antagonists of the invention can be useful as anti-atherosclerotic agents (page 10, lines 4-8). Neither Broze I (or Broze II), Broze III nor Broze IV mention, teach or suggest the treatment of a patient having an atherosclerotic plaque. Thus, Broze I in combination with Broze III and/or Broze IV does not render obvious amended claim 18 and claims depending therefrom.

## SUMMARY

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is strongly encouraged to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and petition for a three-month extension of time and fees. In the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,
GENENTECH, INC.

Date: April 1, 2004 By: 

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